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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/590,054

08/21/2006

Jacob Westman

WESTMAN 3

5605

1444 7590 06/23/2008
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EXAMINER

RAHMANI, NILOOFAR

ART UNIT

PAPER NUMBER

1625

MAIL DATE

DELIVERY MODE

06/23/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/590,054	Applicant(s) WESTMAN ET AL.	
	Examiner NILOOFAR RAHMANI	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 August 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>05/28/2007</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-15 are currently pending in the instant application.

Priority

2. This application was file on 08/21/2006, which is a 371 of PCT/SE05/00412, filed on 03/22/2005, which claims benefit of priority document SWEDEN 0400708-4, filed on 03/22/2004.

3. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "preparing" is confusing. There is no reaction steps to change R¹ and R² to the other R¹ and R² of a compound of formula (I). Correction is required.

4. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, and 11-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to

enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue”. These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

- 1) The breadth of the claims.
- 2) The nature of the invention,
- 3) The state of the prior art,
- 4) The level of one of ordinary skill,
- 5) The level of predictability in the art,
- 6) The amount of direction provided by the inventor,
- 7) The existence of working examples,
- 8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The instant invention is drawn to a method of treating cancer using the formula (I).

The state of the prior art: "Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn

specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, “petri dish cancer” is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.”

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects, whether or not the compounds of formula of claim 1 would be useful for treating a pharmacological condition in a subject.

Amount of guidance/working examples: Applicants provide some examples of tested compounds and WST-1 assay on pages 25-30. However, applicants

provide no guidance for how WST-1 assay could treat any and all known or unknown diseases. There are no examples in the instant specification showing that the instant compounds can treat any diseases.

The breadth of the claims: The breadth of claims is drawn to a method of treating cancer using the formula (I).

The quantity of undue experimentation needed: Since the guidance and teaching provided by the specification is insufficient for treating a mammal having a medical condition associated with WST-1 assay using the compound of formula (I), one of ordinary skill in the art, even with high level of skill, is unable to use the instant compounds as claimed without undue experimentation.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Taking all of the above into consideration, it is not seen where the instant claims 1-2, and 11-15, for treating a mammal having a medical condition associated with WST-1 assay using the compound of formula (I), have been enabled by the instant specification.

5. *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and

to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is not found in the instant specification. c) There is no working example of a prodrug of a compound the formula (I). d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596. in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical

chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim 1 as well as the presently unknown list of potential prodrug derivatives embraced by claim 1.

6. *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

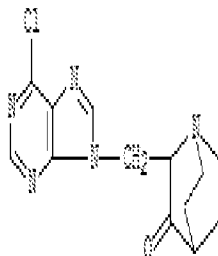
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Bykov et al. WO 2002024692. Bykov et al. discloses the instant claimed compound, which from the STN search is

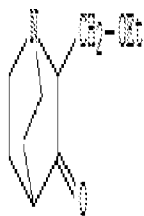
RN 405096-63-1

Art Unit: 1625

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[(6-chloro-9H-purin-9-yl)methyl]-

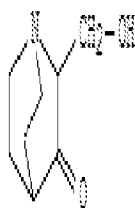
, which anticipates the instant compounds when R^3 is O, R^1 is H, and R^2 is $-\text{CH}_2-\text{N} R^4 R^5$, R^4 and R^5 are bonded together and form, together with the nitrogen atom to which they are bonded, a substituted bicyclic heterocyclyl in the instant application. Therefore, the instant claims are anticipated by Bykov et al.

7. Claims 3, and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Nielsen et al. Journal of Organic Chemistry (1966), 31(4), pages 1053-9. Nielsen et al. discloses the instant claimed compound, which from the STN search is

RN 5291-13-4**CN** 3-Quinuclidinone, 2-(ethoxymethyl)-**RN** 5291-27-0

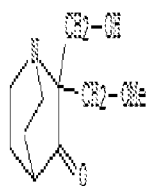
Art Unit: 1625

CN 3-Quinuclidinone, 2-(hydroxymethyl)-



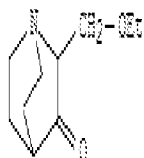
,
RN 5291-32-7

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-(hydroxymethyl)-2-(methoxymethyl)-



,
RN 5291-33-8

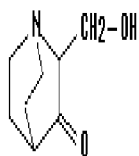
CN 1-Azabicyclo[2.2.2]octan-3-one, 2-(ethoxymethyl)-, compd. with
2,4,6-trinitrophenol



,
RN 5291-35-0

CN 3-Quinuclidinone, 2-(hydroxymethyl)-, hydrochloride

Art Unit: 1625

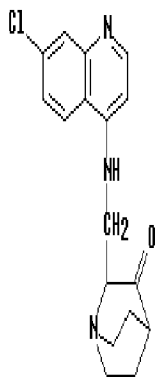


in the instant application. Therefore, the instant claims are anticipated by Nielsen et al.

8. Claims 3, and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Singh et al. Journal of Medicinal Chemistry (1969), 12, pages 524-6. Singh et al. discloses the instant claimed compound, which from the STN search is

RN 21566-68-7

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[[[(7-chloro-4-quinoliny)amino]methyl]-

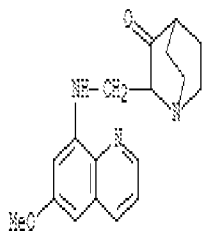


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RN 22776-50-7

CN 3-Quinuclidinone, 2-[[[(6-methoxy-8-quinolyl)amino]methyl]-

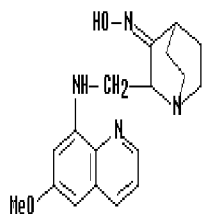
Art Unit: 1625



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RN 22776-52-9

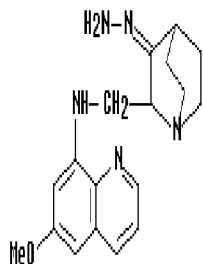
CN 3-Quinuclidinone, 2-[[[(6-methoxy-8-quinolyl)amino]methyl]-, oxime



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RN 22950-03-4

CN 3-Quinuclidinone, 2-[[[(6-methoxy-8-quinolyl)amino]methyl]-, hydrazone



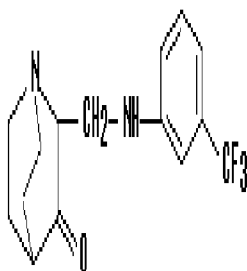
in the instant application. Therefore, the instant claims are anticipated by Singh et al.

Art Unit: 1625

9. Claims 3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Shimizu et al. Bulletin of the Chemical Society of Japan (1973), 46(5), 1520-5. Shimizu et al. discloses the instant claimed compound, which from the STN search is

RN 41971-65-7

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[[[3-(trifluoromethyl)phenyl]amino]methyl]-



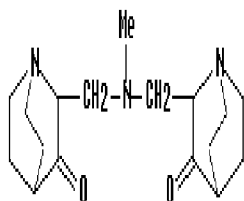
in the instant application. Therefore, the instant claims are anticipated by Shimizu et al.

10. Claims 3-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Elkin et al. US 3726877. Elkin et al. discloses the instant claimed compound, which from the STN search is

RN 19576-25-1

CN 1-Azabicyclo[2.2.2]octan-3-one, 2,2'-[(methylimino)bis(methylene)]bis-

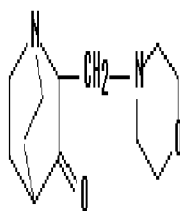
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RN 41971-48-6

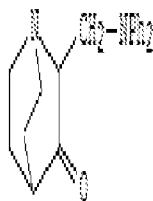
CN 1-Azabicyclo[2.2.2]octan-3-one, 2-(4-morpholinylmethyl)-



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RN 41971-49-7

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[(diphenylamino)methyl]-

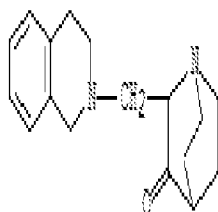


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RN 41971-50-0

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[(3,4-dihydro-2(1H)-isoquinolinyl)methyl]-

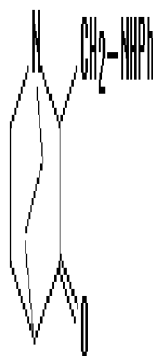
Art Unit: 1625



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RN 41971-51-1

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[(phenylamino)methyl]-

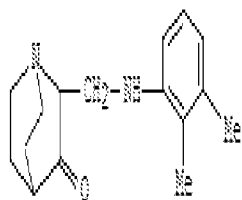


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RN 41971-52-2

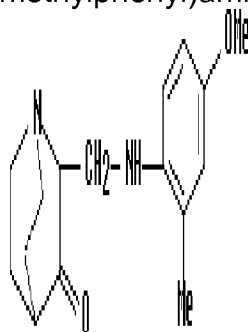
CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[[2,3-dimethylphenyl]amino]methyl]-

Art Unit: 1625



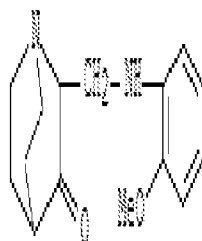
RN' 41971-53-3

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[(4-methoxy-2-methylphenyl)amino]methyl]-



RN' 41971-54-4

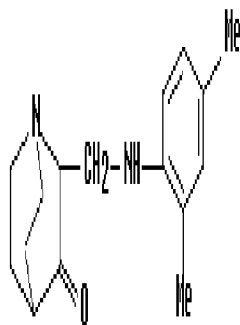
CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[(2-methoxyphenyl)amino]methyl]-



RN' 41971-55-5

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[(2,4-dimethylphenyl)amino]methyl]-

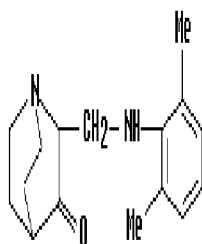
Art Unit: 1625



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RN 41971-57-7

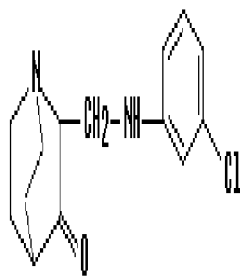
CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[(2,6-dimethylphenyl)amino]methyl-



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RN 41971-59-9

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[(3-chlorophenyl)amino]methyl-

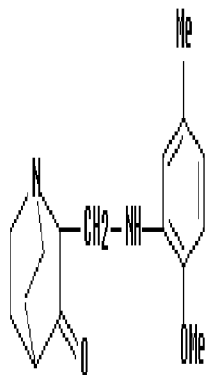


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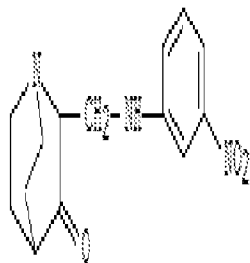
RN 41971-60-2

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[[[(2-methoxy-5-methylphenyl)amino)methyl]-



,
RN 41971-61-3

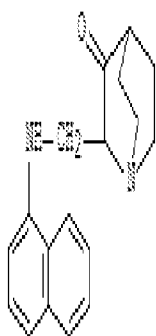
CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[[[(3-nitrophenyl)amino)methyl]-



,
RN 41971-63-5

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[(1-naphthalenylamino)methyl]-

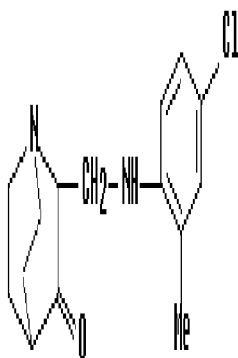
Art Unit: 1625



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RN 41971-64-6

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[[4-chloro-2-methylphenyl]amino]methyl-



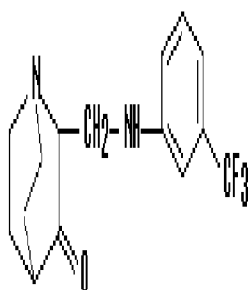
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RN 41971-65-7

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[[[3-(trifluoromethyl)phenyl]amino]methyl]-

Art Unit: 1625

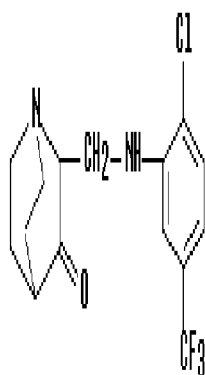
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RN 41971-66-8

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[[[2-chloro-5-(trifluoromethyl)phenyl]amino]methyl]-

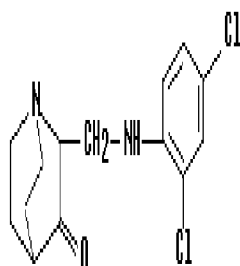


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RN 41971-67-9

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[[[2,4-dichlorophenyl]amino]methyl]-

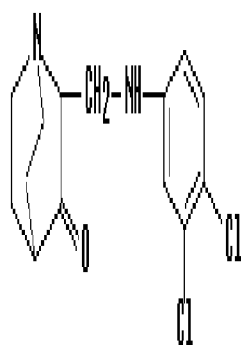
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RN 41971-68-0

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[(3,4-dichlorophenyl)amino]methyl-

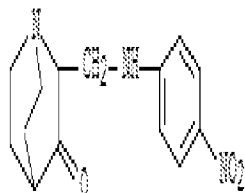


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RN 41971-69-1

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[(4-nitrophenyl)amino]methyl-

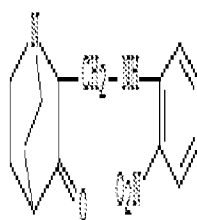
Art Unit: 1625



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RN 41971-70-4

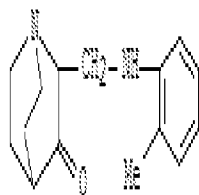
CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[[2-nitrophenyl]amino]methyl-



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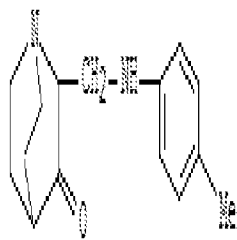
RN 41971-71-5

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[[2-methylphenyl]amino]methyl-



RN 41971-72-6

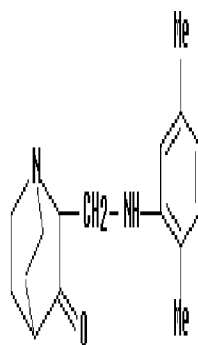
CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[[4-methylphenyl]amino]methyl-



RN 41971-73-7

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[[2,5-dimethylphenyl]amino]methyl-

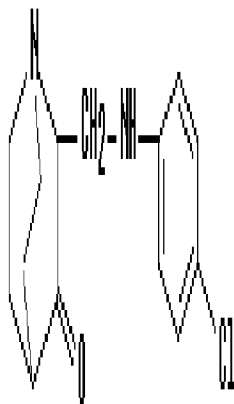
Art Unit: 1625



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RN 42036-83-9

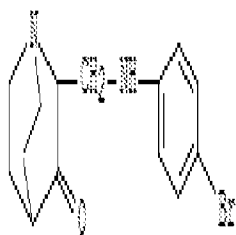
CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[[4-chlorophenyl]amino]methyl-



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RN 42036-85-1

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-[[4-bromophenyl]amino]methyl-

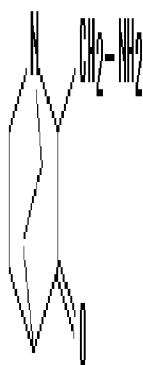


in the instant application. Therefore, the instant claims are anticipated by Elkin et al.

11. Claims 3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Dickinson et al. Univ. Missouri, Rolla, MO, USA, (1972) 118 pp. Avail.: Univ. Microfilms, Ann Arbor, Mich., Order No. 73-17,062, [Diss. Abstr. Int. B 1973, 34(1), 116] (abstract). Dickinson et al. discloses the instant claimed compound, which from the STN search is

RN 42817-38-9

CN 1-Azabicyclo[2.2.2]octan-3-one, 2-(aminomethyl)-



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in the instant application. Therefore, the instant claims are anticipated by Dickinson et al.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Niloofar Rahmani whose telephone number is 571-272-4329. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/NILOOFAR RAHMANI/

06/18/2008

/D. Margaret Seaman/

Primary Examiner, Art Unit 1625